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(54) Title: USE OF VINCA ALKALOYDS, TAXANE, CRYPTOPHYCINE, EPHITOLINE OR ELEUTHEROBINE FOR TREATING ALZHEIMER

(57) Abstract: The present invention relates to medicaments that are useful in the prevention, halting or reversal of Alzheimer's disease progression through the stabilisation of at least one cytoskeletal and/or microtubule stabilising compound.

USE OF VINCA ALKALOYDS, TAXANE, CRYPTOPHYCINE,
EPHITOLINE OR ELEUTHEROBINE FOR TREATING ALZHEIMER

1

2

3

4 The present invention relates to medicaments that
5 are useful in the prevention, halting or reversal of
6 Alzheimer's Disease progression in mammals and these
7 medicaments are cytoskeletal and/or microtubule
8 stabilisers.

9

10 Alzheimer's Disease (AD) is a chronic debilitating
11 and devastating neurodegenerative disorder, that
12 gives rise to failure of all but the most primitive
13 cognitive functions. As AD is predominately present
14 in patients over the age of 65, this particular
15 disease will become a massive problem for society as
16 society's average age increases in the medium term.

17

18

1 AD is diagnosed by the presence in brain tissue of
2 extra cellular plaques that are mainly composed of
3 β -amyloid ($A\beta$) that is produced by proteolytic
4 processing of a longer transmembrane protein, the
5 Alzheimer Precursor Protein (APP), see Figure 1.
6
7 Importantly however, there also exists intracellular
8 aggregations of a microtubule binding protein called
9 Tau that has been aberrantly modified in a number of
10 ways, the most common being hyper-phosphorylation.
11 These modifications induce Tau to aggregate into
12 insoluble helical rods termed Paired Helical
13 Filaments (PHF).
14
15 Currently two main theories exist in the field of AD
16 research that explain the aetiology and progression
17 of this disease. The first and most widely accepted
18 is the amyloid cascade hypothesis. This hypothesis
19 argues that there is a strong genetic influence, as
20 in autosomal dominant disease mutations in the APP
21 and presenilin genes give rise to the increased
22 production of $A\beta$. Furthermore the extra cellular
23 presence of $A\beta$ (a neuro-toxin) in the brain tissue
24 of AD patients explains the symptoms of AD caused by
25 extensive neuronal cell death. This is supported by
26 the observation that Down Syndrome patients who all
27 have an additional copy of the APP gene, develop AD-
28 like pathology from their early thirties. However,
29 vaccines directed against $A\beta$ were found to initiate
30 a potentially lethal, inflammatory immune response
31 in humans, which was not seen in the murine models.
32

1 The second theory involves the intracellular
2 aggregation of the Tau protein. Abnormal
3 phosphorylation of this protein, which plays a major
4 role in intracellular protein trafficking, inhibits
5 normal cellular functioning and causes eventual cell
6 death. APP has not yet been implicated in this
7 mechanism.

8
9 A recent finding by Roncarati et al (Proc Natl Acad
10 Sci U S A. 2002 May 14;99(10):7102-7107) shows that
11 the C-terminus of the APP protein plays a role in
12 protein movement in cells via attachment to kinesin
13 via the kinesin light chain (KLC) molecular motor,
14 see Figure 2. The present inventors have developed
15 a new, non-obvious unifying mechanism that
16 incorporates the two above-mentioned hypotheses,
17 explaining how APP and Tau are involved in AD
18 progression.

19
20 It is already known that the APP protein is
21 proteolytically cleaved by α , β and γ secretases
22 (see Figure 1) and that α secretase cleaves APP
23 towards the middle of A β sequence. This enzyme is of
24 little consequence here. However β secretase,
25 (Vassar et al Science, 1999 Oct, 286 (5440): 735-
26 41), cleaves the last 100 amino acid residue of the
27 APP C-terminus and this is further cleaved by the
28 γ secretase to produce the A β peptide. The β
29 secretase activity is known to be rate limiting step
30 in this process. As yet the γ secretase is not
31 characterised fully but the presenilin family of

1 proteins are known to be involved (Vassar R, J. Mol
2 Neuroscience, 2001 Oct, 17(2):157-70).

3
4
5 It is proposed herein that the β and γ secretases
6 are active in the detachment of intracellular
7 vesicles from the molecular motors bound to the C-
8 terminus of APP. Therefore in the event of abnormal
9 APP degradation, leading to increased APP C-terminus
10 levels in the cytoplasm, inevitable destabilisation
11 of the intracellular trafficking system would
12 eventually cause cell death. As the molecular motor
13 bound to APP only binds to β -tubulin, the amount of
14 available β -tubulin would decrease and the amount of
15 available α -tubulin may increase or remain the same
16 by biochemical negative and positive feed back
17 mechanisms, respectively. Destabilisation of the
18 microtubular network in the cell would give rise to
19 increased levels of *Tau*, inducing PHF production by
20 *Tau* hyper-phosphorylation. This combined with the
21 presence of increased APP C-terminus would lead to
22 higher levels of $A\beta$, as the γ secretase is not rate
23 limiting. The cell would then export these
24 $A\beta$ residues into the extra-cellular space in order to
25 reduce the intra-cellular concentration. As $A\beta$ is
26 neurotoxic, an inflammatory response is initiated
27 leading to neurodegeneration and typical AD
28 symptoms. However, the intracellular effects of $A\beta$ on
29 cellular metabolism, and more specifically vesicle
30 trafficking is what this particular invention is
31 concerned with.

1
2 With this in mind an object of the present invention
3 is to stabilise the microtubular network in cells
4 using known and/or new cytoskeletal stabilising
5 compounds, so that the actions and effects of A β can
6 be overcome. Some currently used anti-cancer drugs
7 work by stabilising microtubules in cells, thereby
8 lethally preventing mitosis, and we intend to show
9 their ability to prevent, halt or reverse the
10 biological activity of the A β peptide. Therefore,
11 it is an object of the present invention to provide
12 a medicament to prevent, limit or halt the
13 progression of Alzheimer's Disease.

14

15 According to the present invention there is provided
16 a medicament to prevent, limit or halt the
17 progression of Alzheimer's Disease in patients, the
18 medicament including at least one cytoskeletal-
19 stabilising agent.

20

21 Cytoskeletal components of the cell are deemed to
22 include actin filaments, microtubules and
23 intermediate filaments.

24

25 Preferably the cytoskeletal agent is at least one
26 microtubule stabilising agent.

27

28 Preferably the cytoskeletal agent is at least one
29 actin stabilising agent.

30

1 Preferably the medicament is a combination of at
2 least one cytoskeletal stabilising agent and/or at
3 least one microtubule stabilising agent.

4

5

6 Preferably the medicament includes a Vinca alkaloid,
7 a taxane, a cryptophycine, epothilone or an
8 eleutherobine.

9

10 Preferably the medicament is an inhibitor of
11 microtubule destabilisers.

12

13 The invention thus provides the use of any of these
14 agents in the preparation of a medicament for the
15 treatment of Alzheimer's Disease.

16

17 Most preferably the medicament is or includes
18 Taxol™.

19

20 Preferably the medicament inhibits the abnormal
21 phosphorylation of the Tau protein. Abnormal
22 phosphorylation includes hyperphosphorylation of the
23 Tau protein.

24

25 Preferably the medicament inhibits abnormal
26 degradation of the Amyloid Precursor Protein and
27 inhibits intra cellular build up of the A β peptide.
28 Abnormal degradation of APP includes degradation of
29 APP according to the amyloid pathway as opposed to
30 the neutrophic pathway.

31

1 Preferably the medicament is specifically targeted
2 to the brain. To target the medicament to the brain
3 the medicament preferably is able to cross the blood
4 brain barrier.

5

6

7 According to a further aspect of the present
8 invention there is provided a medicament including
9 Trk A, or an analogue thereof including a family
10 member Trk B or Trk C.

11

12 According to another aspect of the present invention
13 there is provided the use of Trk A, or an analogue
14 thereof including a family member Trk B or Trk C in
15 the preparation of a medicament for the treatment of
16 Alzheimer's disease.

17

18 An agent includes a small molecule, compound,
19 protein or part thereof.

20

21 Embodiments of the present invention will now be
22 described, by way of example only, with reference to
23 the accompanying drawings in which.

24

25 Figure 1 is a diagrammatic representation of
26 the Amyloid Precursor Protein (APP);

27

28 Figure 2 is a diagrammatic representation of
29 the APP protein of Figure 1, bound to kinesin,
30 via the kinesin light chain, showing kinesin
31 "walking" along a microtubule by selective

1 binding of the kinesin heavy chain to β tubulin
2 submits of the microtubule;

3
4 Figure 3 is a Western Blot showing decreased
5 levels of kinesin light chain C (60-70 kDa) in
6 the presence of increasing expression levels of
7 the A β peptide;

8
9 Figure 4 is a diagrammatic representation of
10 the Western Blot of figure 4a showing decreased
11 levels of kinesin light chain C (60-70 kDa) in
12 the presence of increasing expression levels of
13 the A β peptide;

14
15 Figure 5a is a Western Blot showing decreased
16 levels of β tubulin (55kDa) and increasing
17 levels of Amyloid β (4kDa) in the presence of
18 increasing expression levels of the A β peptide;

19
20 Figure 5b is a diagrammatic representation of
21 the Western Blot of figure 5a showing decreased
22 levels of β tubulin (55kDa) and increasing
23 levels of Amyloid β (4kDa) in the presence of
24 increasing expression levels of the A β peptide;

25
26 Figure 6 is a diagrammatic representation of
27 the Western Blot showing decreasing levels of
28 TrkA (140kDa) in the presence of increasing
29 expression levels of the A β peptide;

30

1 Figure 7 is a Western Blot showing increased
2 levels of PHF - Tau in response to increased
3 expression levels of A β peptide; and

4
5 Figure 8 is a Western Blot showing decreased
6 levels of TRK A in response to a mutation of
7 PS2.

8
9
10 As shown in Figure 1 the Amyloid Precursor Protein
11 (APP) is a transmembrane protein that undergoes
12 endoproteolysis by three proteases called α , β and γ -
13 secretase. After complete processing of the APP
14 protein, the β -amyloid 42 amino acid peptide is
15 released intracellularly.

16
17 Figure 2 is a diagrammatic representation of APP
18 binding to the kinesin light chain of the molecular
19 motor kinesin. Kinesin "walks" selectively along a
20 microtubule by binding selectively to β -tubulin via
21 its kinesin heavy chain subunit.

22
23 Figure 3 is a picture of a representative Western
24 Blot for kinesin light chain of protein extracts
25 from cells expressing no A β peptide (lane 1);
26 constitutively low expression of A β peptide cells
27 (lane 2) and constitutively high expression of A β
28 peptide cells (lane 3), i.e. transfected with the
29 vector constitutively encoding the C100 peptide;
30 wherein down regulation of kinesin light chain is
31 obvious in lane 3.

1
2 Figure 4 is a drawing of a representative Western
3 Blot for kinesin light chain of protein extracts
4 from cells expressing no A β peptide (lane 1);
5 constitutively low expression of A β peptide cells
6 (lane 2) and constitutively high expression of A β
7 peptide cells (lane 3), i.e. transfected with the
8 vector constitutively encoding the C100 peptide;
9 wherein down regulation of kinesin light chain is
10 obvious in lane 3.

11
12 Figure 5b is another Western Blot for β -tubulin of
13 the same cells as shown in Figure 4b where it is
14 clear that the β -tubulin concentration decreases
15 while amyloid β protein increases accordingly.
16 Furthermore, as shown in figure 6, levels of a nerve
17 growth factor receptor Trk A, carried by vesicles
18 that use APP to connect to a molecular motor, are
19 also decreased in a A β peptide concentration
20 dependent manner.

21
22 As shown in figure 8, one of the primary
23 neurotrophic molecules Trk A is decreased when a PS2
24 mutation is introduced in a cell line. The level of
25 Trk A is also found to be decreased in cell lines
26 having a PS1 mutation or a mutation in APP leading
27 to an increase in the A β expression.

28
29 Trk A is a receptor which upon ligand binding is
30 internalised and translocates from the cellular
31 membrane to the nucleus of the cell. The presence

1 of Trk A in the nucleus causes the cell to continue
2 to survive whereas a lack of Trk A in the nucleus
3 promotes cell degradation. Trk A relies on
4 cytoskeletal proteins for transport and thus
5 disruption of the cytoskeletal proteins, as set out
6 above, would decrease the level of Trk A being moved
7 to the nucleus. As the movement of Trk A to the
8 nucleus would be limited by disruption of
9 cytoskeletal proteins, it is proposed to provide Trk
10 A, family members Trk B or Trk C or an analogue
11 thereof to the nucleus to promote cellular survival.

12

13 Figure 7 shows clearly increased levels of PHF-Tau
14 due to the increasing levels of the A β peptide
15 intracellularly.

16

17 Presenilin-mutated cell lines were looked at under
18 the exact same conditions and show clearly that A β
19 is involved in the manifestation of diseases arising
20 from these mutations.

21

22 Components of the cell that bind to the A β peptide
23 more specifically will be investigated using
24 standard methods, including specific chemical cross
25 linking of the C100 and/or A β peptide in the living
26 cell or using cell free systems.

27

28 The possibility that the C100 peptide and/or A β may
29 have some transcriptional control activity will be
30 investigated by detecting its presence in the
31 nucleus and its ability to complex with Tip60. The

1 protein profile of these cells will be analysed
2 using high-resolution 2D gel electrophoresis and Q-
3 TOF and/or MALDI TOF Mass Spec. The mRNA profile
4 will be analysed using expression chips commonly
5 known in this field of research.

6
7 The aim of the above experiments is to elucidate the
8 complete mechanism of action of the C100 and A β
9 peptides, so that the counter active activity of
10 tubulin stabilising compounds like Taxol™ can be
11 analysed.

12
13 An experiment in the process of being carried out is
14 the use of magnetic beads with Anti- A β antibodies
15 bound to them, which are then to be added to semi
16 permeabilised cells that have been transfected with
17 the constitutively expressed C100 peptide encoding
18 vector, and these experiments will be repeated on
19 control cells as well as the above transfected cells
20 incubated with drugs like Taxol etc.

21
22 The constitutively expressed C100 peptide vector
23 does not allow for the regulation or switching on
24 and off of the expression of the C100 peptide
25 described above.

26
27 The present inventors shall also investigate the
28 role proteins like OP18 and Rb3 may play in the
29 aetiology of AD, as they are known microtubule
30 destabilisers proteins. The effect of microtubule
31 destabilisers in an essential part of further
32 investigation.

1 Various modifications can be made without departing
2 from the scope of the invention, for example, ways
3 of negating the effect of microtubule destabilisers
4 would elicit the same effect as medicaments to
5 stabilise cytoskeletal proteins. Suitable
6 inhibitors of microtubule destabilisers would be
7 known to those in the art.

1 **Claims**

2

3 1. A medicament to prevent, limit or halt the
4 progression of Alzheimer's Disease the medicament
5 including at least one cytoskeletal-stabilising
6 agent.

7

8 2. A medicament as claimed in claim 1 to prevent,
9 limit or halt the progression of Alzheimer's Disease
10 the medicament including at least one inhibitor to
11 microtubule destabilisers.

12

13 3. A medicament as claimed in claim 1 or 2 wherein
14 the medicament is a combination of at least one
15 cytoskeletal stabilising agent and/or at least one
16 microtubule stabilising agent.

17

18 4. A medicament as claimed in claim 1 to 3 wherein
19 the medicament includes a Vinca alkaloid, a taxane,
20 a cryptophycine, epothilone or an eleutherobine.

21

22 5. A medicament as claimed in claim 1 to 4 wherein
23 the medicament inhibits the abnormal phosphorylation
24 of the Tau protein.

25

26 6. A medicament as claimed in claim 1 to 5 wherein
27 the medicament inhibits abnormal degradation of the
28 Amyloid Precursor Protein and inhibits intra
29 cellular build up of the A β peptide.

30

31 7. A medicament to prevent, limit or halt the
32 progression of Alzheimer's Disease the medicament

1 including Trk A, or an analogue thereof including a
2 family member Trk B or Trk C.

3

4 7. A medicament as claimed in any preceeding claim
5 wherein the medicament is specifically targeted to
6 the brain.

7

8 8. Use of at least one cytoskeletal stabilising
9 agent and/or at least one microtubule stabilising
10 agent in the preparation of a medicament for the
11 treatment of Alzheimer's Disease.

12

13 9. Use of at least one inhibitor of microtubule
14 destabilisers in the preparation of a medicament for
15 the treatment of Alzheimer's Disease.

16

17 10. Use of Trk A, or an analogue thereof including
18 a family member Trk B or Trk C in the preparatio of
19 a medicament for the treatment of Alzheimer's
20 Disease.

1/9

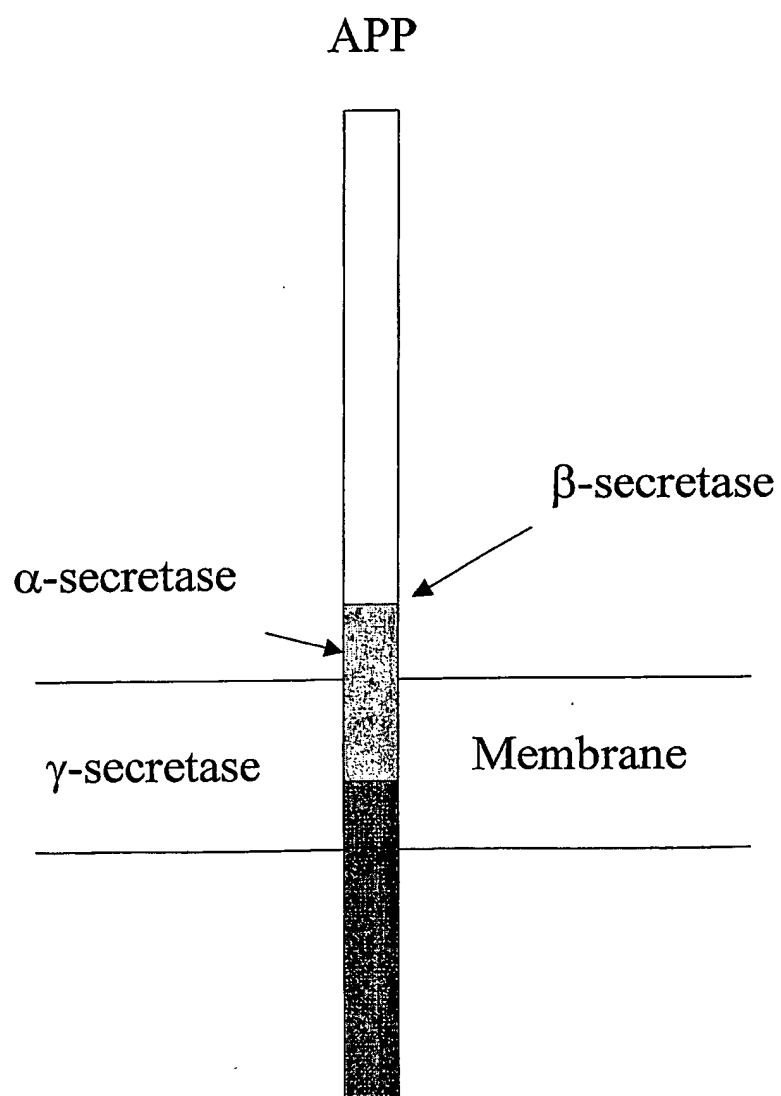


Figure 1

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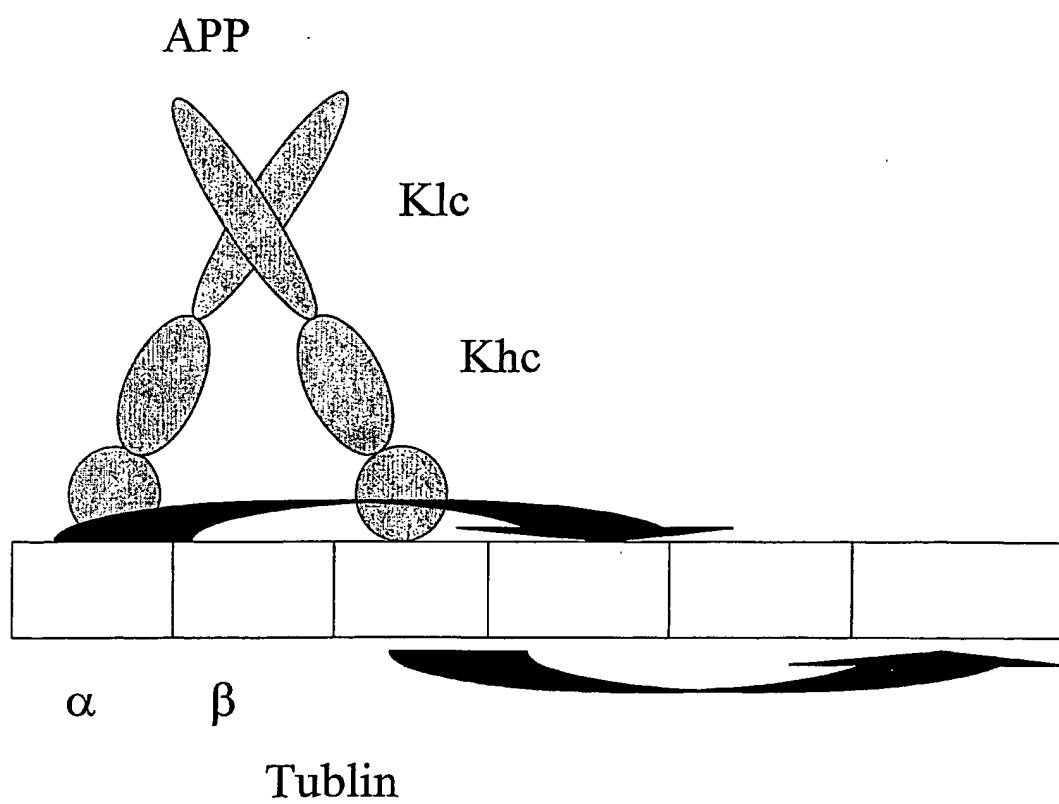
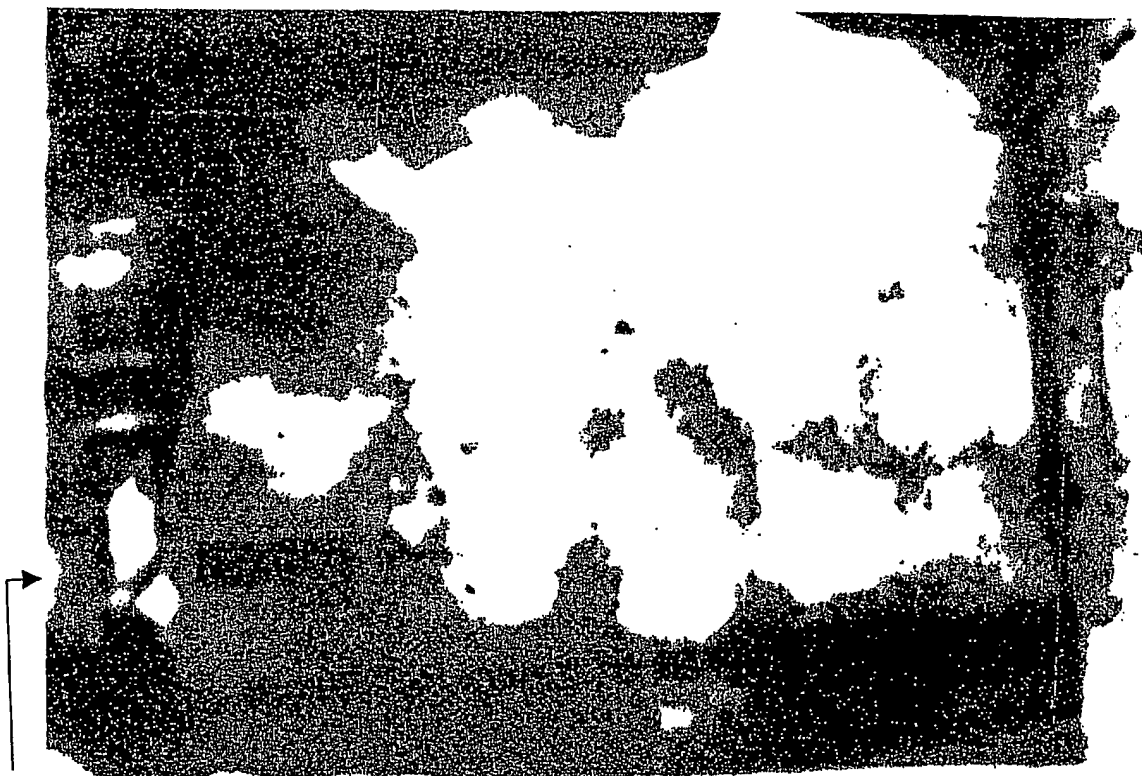


Figure 2

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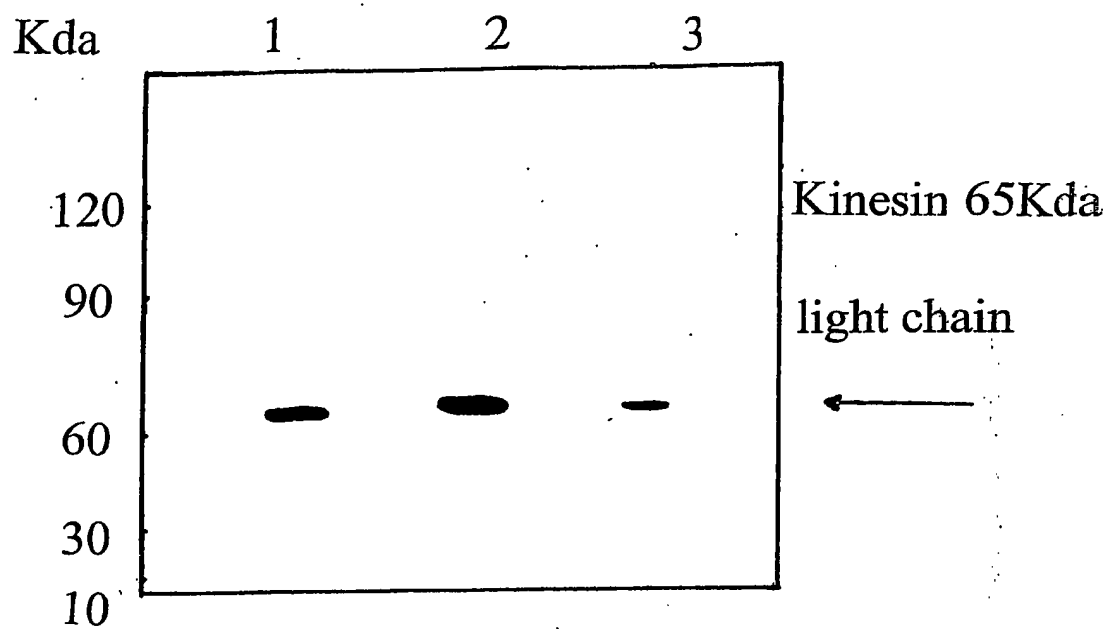
Figure 3



Kinesin

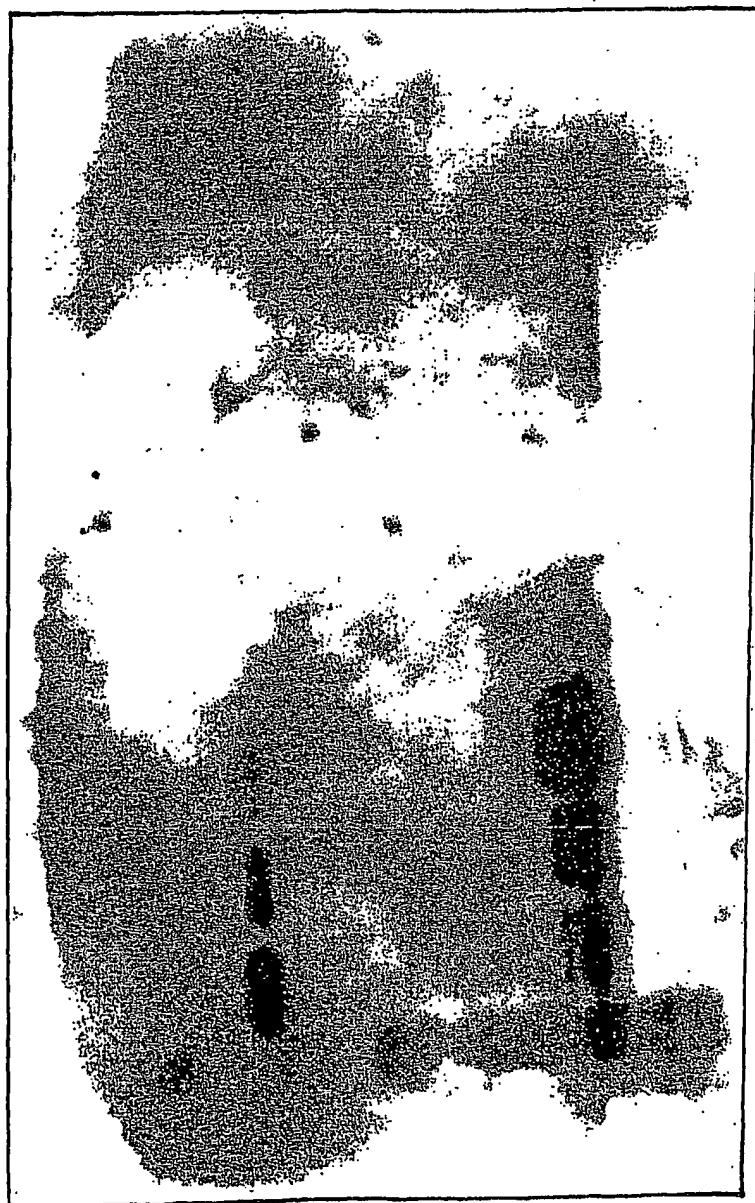
4/9

Figure 4



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Figure 5a

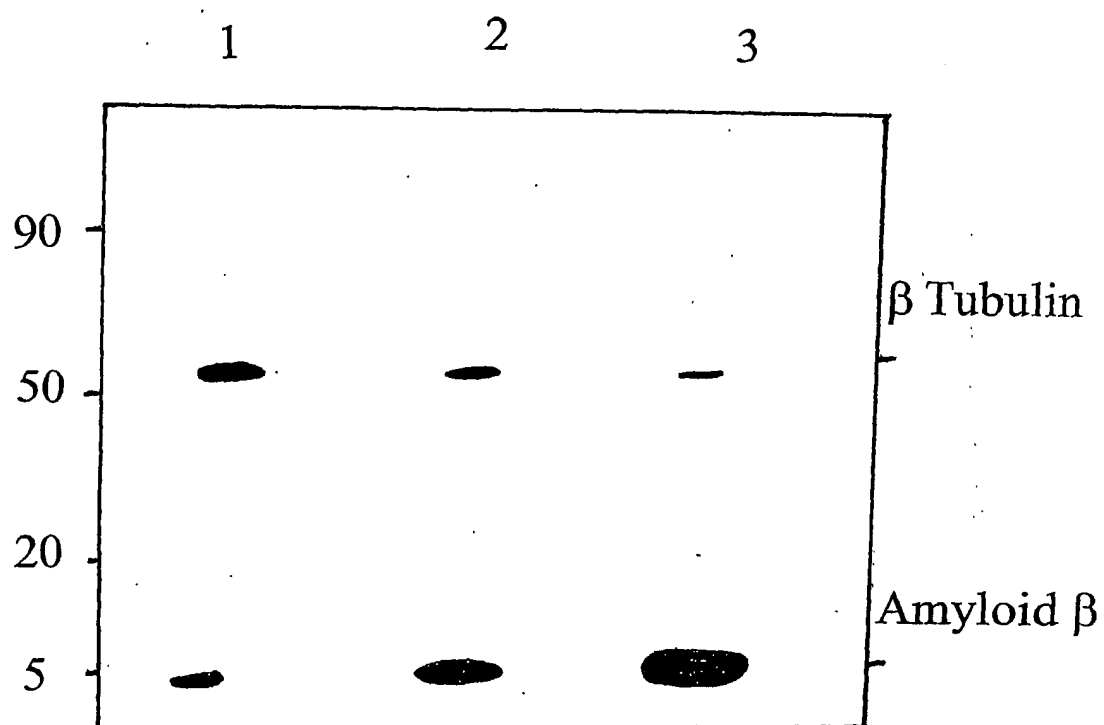


β Tub

A β

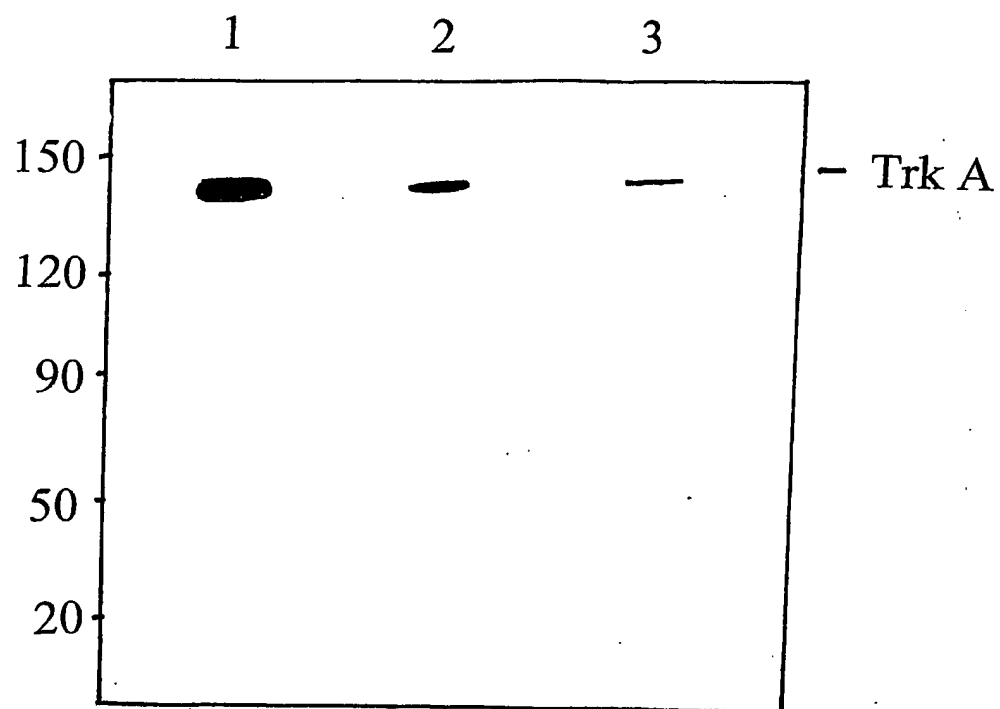
6/9

Figure 5b



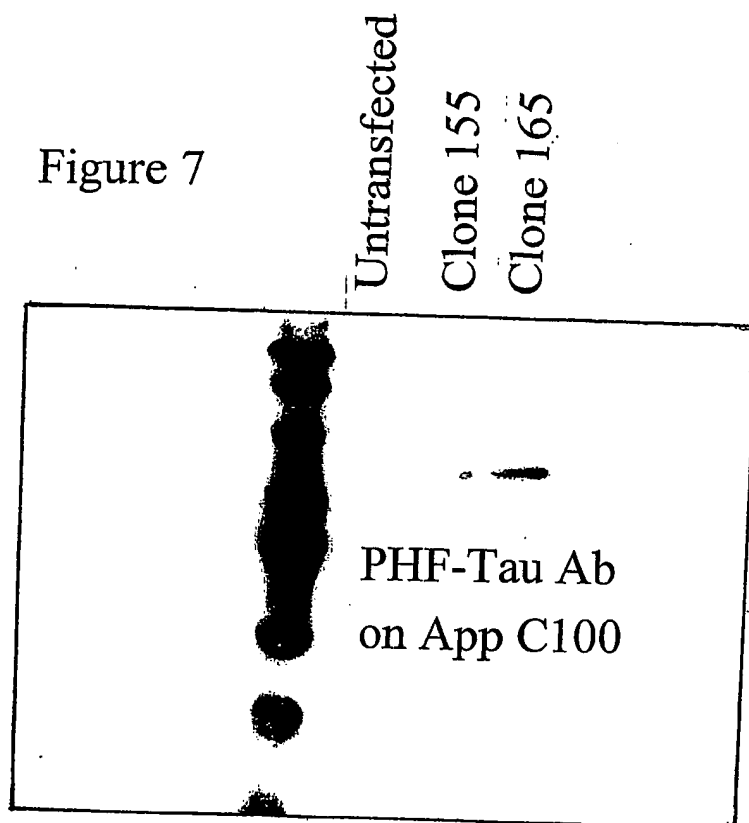
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Figure 6



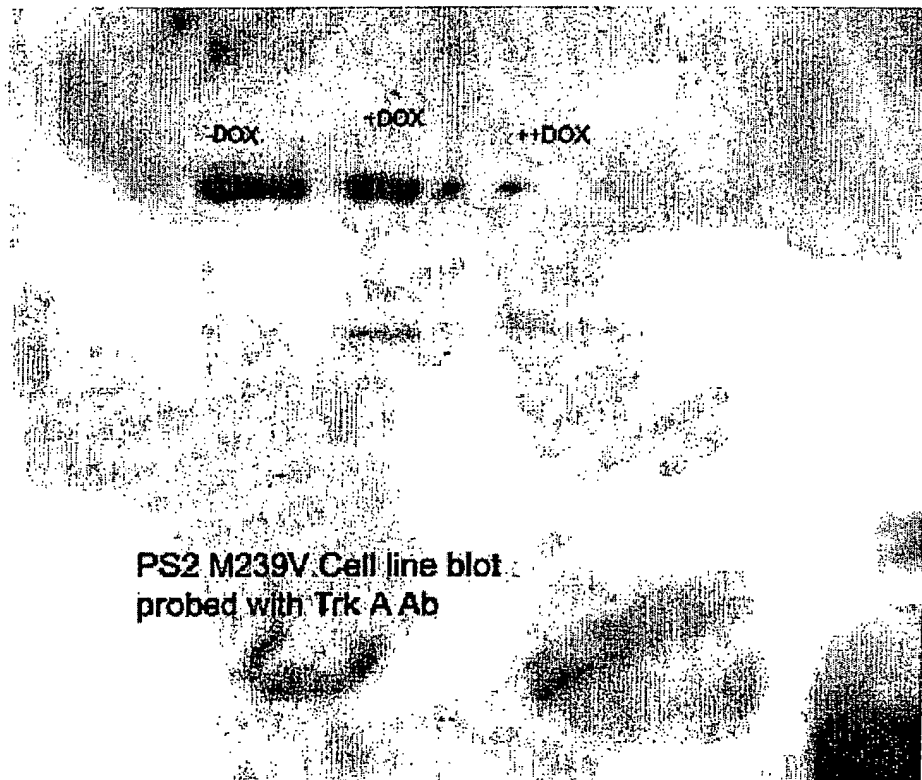
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Figure 7



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Figure 8



INTERNATIONAL SEARCH REPORT

International Application No
PC1/GB 03/03601

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/475 A61K31/337 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, MEDLINE, SCISEARCH, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LI G ET AL: "STABILIZATION OF THE CYCLIN - DEPENDENT KINASE 5 ACTIVATOR, P35, BY PACLITAXEL DECREASES BETA - AMYLOID TOXICITY IN CORTICAL NEURONS." SOCIETY FOR NEUROSCIENCE ABSTRACT VIEWER AND ITINERARY PLANNER, vol. 2002, 2002, page Abstract No. 591.9 XP001172845 32nd Annual Meeting of the Society for Neuroscience;Orlando, Florida, USA; November 02-07, 2002 the whole document</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>1,2,4-6, 9-11</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

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PC1/GB 03/03601

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	POLLACK S J ET AL: "Natural product-derived small molecule activators of the Trk neurotrophin receptors" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 27, no. 1, 2001, page 356 XP001172844 31st Annual Meeting of the Society for Neuroscience; San Diego, California, USA; November 10-15, 2001 ISSN: 0190-5295 the whole document	
X	ADLARD PAUL A ET AL: "The effects of taxol on the central nervous system response to physical injury" ACTA NEUROPATHOLOGICA, vol. 100, no. 2, August 2000 (2000-08), pages 183-188, XP001173124 ISSN: 0001-6322 page 183, column 2, line 12 - line 30 page 184, column 1, paragraph 3 page 187, column 2, paragraph 3	1,2,4-6, 8-11
X	FURUKAWA K ET AL: "A microtubule stabilizing compound, taxol, attenuates neuronal vulnerability of tau mutations in FTDP-17" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 27, no. 1, 2001, page 922 XP001173123 31st Annual Meeting of the Society for Neuroscience; San Diego, California, USA; November 10-15, 2001 ISSN: 0190-5295 the whole document	1,2,4-6, 9-11
A	BOISSIÈRE F ET AL: "Trk neurotrophin receptors in cholinergic neurons of patients with Alzheimer's disease." DEMENTIA AND GERIATRIC COGNITIVE DISORDERS. SWITZERLAND 1997 JAN-FEB, vol. 8, no. 1, January 1997 (1997-01), pages 1-8, XP008024311 ISSN: 1420-8008 page 7, column 2, paragraph 2	7
P,X	RICE ANTONIE ET AL: "Overcoming the blood-brain barrier to taxane delivery for neurodegenerative diseases and brain tumors." JOURNAL OF MOLECULAR NEUROSCIENCE, vol. 20, no. 3, 2003, pages 339-343, XP008024299 ISSN: 0895-8696 (ISSN online) page 339, column 1, line 1 - column 2, line 2 page 343, column 1, paragraph 1	8

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KIDD P M: "A review of nutrients and botanicals in the integrative management of cognitive dysfunction." ALTERNATIVE MEDICINE REVIEW: A JOURNAL OF CLINICAL THERAPEUTIC. UNITED STATES JUN 1999, vol. 4, no. 3, June 1999 (1999-06), pages 144-161, XP008024312 ISSN: 1089-5159 page 151, column 1, paragraph 4 -column 2, paragraph 2 ---	
A	LEMAIRE LAURENT ET AL: "Magnetic resonance imaging of the neuroprotective effect of Xaliproden in rats" INVESTIGATIVE RADIOLOGY, vol. 37, no. 6, June 2002 (2002-06), pages 321-327, XP008024309 ISSN: 0020-9996 abstract ---	
X	EP 0 870 510 A (LILLY CO ELI) 14 October 1998 (1998-10-14) page 2, paragraph 1 claim 17 ---	1-8
A	CINEL B ET AL: "Solid-state and solution conformations of eleutherobin obtained from X-ray diffraction analysis and solution NOE data" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 41, no. 16, April 2000 (2000-04), pages 2811-2815, XP004195677 ISSN: 0040-4039 page 2811, paragraph 1 ---	4
A	GIANNAKAKOU PARASKEVI ET AL: "A common pharmacophore for epothilone and taxanes: Molecular basis for drug resistance conferred by tubulin mutations in human cancer cells" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 97, no. 6, 14 March 2000 (2000-03-14), pages 2904-2909, XP002189845 ISSN: 0027-8424 page 2904, column 1, paragraph 1 abstract -----	4

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 03/03601

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-3,5, and 8,9,10 encompass a genus of compounds defined only by their function (cytoskeletal stabilising agent and microtubule destabiliser), wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. Therefore this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope not fully possible (Articles 5, 6 PCT).

Claims 4-6,8 relate to an extremely large number of possible compounds (taxanes, Vinca alkaloids, cryptophycines, eleutherobines). Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). It is not clear to which compounds exactly the protection is sought. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Present claim 8 (if corrected numeration applies) relates to a compound or a combination of compounds defined by reference to a desirable characteristic or property, namely the specific targeting to the brain. Nothing is said in the application, to explain how such a characteristic is achieved. In the present case, the claim so lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the composition by reference to its pharmacocynetic profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds taxol, vincristine vinblastine, cryptophycine, epothilone and eleutorobine, and to trk for the treatment of Alzheimer disease.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 03/03601

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0870510	A	14-10-1998	AU 7104798 A	11-11-1998
			EP 0870510 A2	14-10-1998
			WO 9846193 A2	22-10-1998
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